Association of gamma-glutamyl transpherase activity with electrocardiographic indicators in coronary artery disease patients

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1. Introduction
Gamma-glutamyl transpherase (GGT) is a common test that is used as a liver function indicator and plays an important role in antioxidant defense systems. The main function of GGT is to provide intracellular support for glutathione precursors, which work as intracellular antioxidants, and to catalyze the first step in the degradation of GSH (Whitfield, 2001). The results of clinical studies on individuals with coronary artery disease (CAD) show that GGT activity is directly associated with the oxidative process that contributes to atheromatous plaque formation (Lee et al., 2004; Paolicchi et al., 2004; Emdin et al., 2005; Ulus et al., 2007; Bradley et al., 2014; Kunutsor et al., 2014). GGT appears to be a strong predictor of acute coronary events aside from cardiovascular risk factors (Paolicchi et al., 2004; Ulus et al., 2007; Bradley et al., 2014; Kunutsor et al., 2014).

Apart from coronary artery disease, arrhythmias, especially atrial fibrillation, are frequently seen in clinical practice and cause deterioration in quality of life, morbidity, and mortality.
The risk of arrhythmia can be decreased by various treatment options in patients showing increased risk factors.

In the present study, the association of serum GGT activity with electrocardiographic data was investigated in the CAD population.

2. Material and methods

Patient selection
Data from randomly selected patients who had diagnostic coronary angiography at our institution were analyzed. A total of 254 patients with angiographically diagnosed CAD were included in the study. The clinical presentation was acute coronary syndromes (ACS) in 170 patients. Forty percent (n=68) of patients with ACS were diagnosed as unstable angina (UA), whereas others (60%, n=102) were diagnosed as acute myocardial infarction (MI; all of them were non-ST elevation MI). We performed coronary angiography in 84 patients because of suspected coronary artery disease (exercise stress test and thallium scintigraphy were positive in 60 and 24 patients, respectively). Patients with other cardiac diseases (valvular heart disease, atrial fibrillation, congenital heart disease and aortic aneurysm) who underwent coronary angiography were not included in the study.

CAD was diagnosed via an angiogram and detection of at least 50% stenosis in epicardial coronary arteries or their major branches was considered as CAD. The exclusion criteria for the study were as follows: a history of liver disease, chronic alcohol use, bundle branch block, the presence of a permanent pacemaker, preexcitation syndrome, antiarrhythmic medication use, interventricular and intraventricular conduction delays, and the presence of angina symptoms during recording. Patients with blood pressure in excess of 140/90 mmHg or receiving antihypertensive treatment were considered hypertensive. Likewise, patients with a history of diabetes mellitus, antidiabetic medication use, or a fasting blood glucose level of 126 mg/dl or more were considered diabetic. Prior to every procedure, signed consent was obtained from all of the patients.

GGT measurement
Serum GGT levels were measured at 37 °C by means of an enzymatic calorimetric test using a Roche/Hitachi analyzer. L-gamma-glutamyl-3-carboxy-4-nitroanilide was used as substrate (Mannheim, Germany) (Persijn and van der Slik, 1976). In our laboratory, the normal reference value of the GGT level for a healthy individual was 7-49 U/l.

Electrocardiographic evaluation
All of the patients had a 12-lead resting ECG in a supine position recorded using an analog system. The recording rate was 50 mm/sec with a 10mm/mV gain. The measurements were obtained using a millimetric ruler by an investigator who was unaware of the patient data (The CSE Working Party, 1985). All parameters were measured in all leads and for two consecutive cycles, and the average value was taken for each lead. Sokolow-Lyon voltage (SLV) was calculated as the sum of the S-wave voltage in the V1 or V2 leads and the R-wave voltage in V5 or V6 (the higher of the two) (Sokolow and Lyon 1949). Cornell voltage (CV) was measured in millimeters as the sum of the R-wave voltage in the aVL lead and the S-wave voltage in the V3 lead. Cornell product (CP) was calculated by multiplying the duration of QRS and CV (millimeter x millisecond) (Molloy et al., 1992).

The beginning of the P-wave was considered as the joint between the isoelectric line and first prominent upward or downward incline of the trace. The return of the trace to the isoelectric line was defined to be the end of the P-wave. The difference between the longest and shortest P-waves was defined as P-wave dispersion (PWD).

QT interval was obtained through manual measurement of the time between the beginning of the QRS complex and the point of return to the isoelectric line (the end of the T-wave) in milliseconds. Corrected QT (QTc) was obtained by correcting the QT interval based on the patient’s heart rate (QT interval / √ (RR interval)). QT dispersion (QTd) was defined as the difference between the longest and the shortest QT in each derivation.

Echocardiography
Echocardiographic evaluation was done in the left lateral decubitus position (Vingmed System V, Horten, Norway). The measurements of the left ventricle diameter, wall thickness, and ejection fraction (EF) were obtained according to the device manual (Chetilin et al., 1997).

Coronary Angiography
Coronary angiographies were carried out using Siemens Axiom Artis (Munich, Germany) digital angiography equipment. Selective coronary angiography was performed via the right femoral artery by using the Judkins technique. Coronary arteries were imaged by utilizing right and left anterior oblique views with cranial and caudal positions. At least 50% stenosis in epicardial coronary arteries or their major branches was defined as CAD. Coronary angiographies were evaluated and reported by at least two experienced cardiologists who did not have information about the study.

Statistical analysis
Continuous variables were expressed as mean ± SD. The
distribution of continuous variables for normality was tested using the Kolmogorov-Smirnov test. Logarithmic conversion was performed for non-normally distributed variables based on this evaluation. The groups were compared using the Student t test, while the Pearson test was used to evaluate the association between the constant variables. The indicators of GGT activity were investigated using an analysis of multi-variable regression. A p value less than 0.05 was considered statistically significant.

Reproducibility analysis was performed for intra-observer and inter-observer variability at electrocardiographic measurements (Sokolow-Lyon voltage, Cornell voltage, Cornell product, Corrected QT, QT dispersion, P-wave dispersion) and ejection fraction.

3. Results
A total of 254 patients (174 males, mean age 62 ± 8 years) with angiographically diagnosed CAD were included in the present study. The risk factors for coronary artery disease were diabetes in 76 (29.9%) patients, hypertension in 123 (48.4%) patients, and smoking in 121 (47.6%) patients.

A positive correlation was found between GGT levels and PWD (r = 0.299, p < 0.0001); however, there was a negative correlation between GGT and EF (r = 0.216, p < 0.001). On the other hand, no correlation was found between GGT and the following: SLV, CV, CP, QTc, and QTd (p values are 0.728, 0.892, 0.551, 0.069, and 0.146, respectively).

When the patients were grouped according to gender, a significant association of GGT with PDD and ejection fraction was observed in both of the groups. Nonetheless, a significant correlation between GGT and QTc was only found in the female group (Table 1).

Table 1. Correlation of GGT level with electrocardiographic parameters and ejection fraction in the female and male groups.

<table>
<thead>
<tr>
<th></th>
<th>Male</th>
<th>Female</th>
<th>p value</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sokolow-Lyon voltage (mm)</td>
<td>0.070</td>
<td>0.374</td>
<td>0.056</td>
<td>0.660</td>
</tr>
<tr>
<td>Cornell voltage (mm)</td>
<td>- 0.029</td>
<td>0.712</td>
<td>0.062</td>
<td>0.622</td>
</tr>
<tr>
<td>Cornell product (mm.sc)</td>
<td>0.021</td>
<td>0.792</td>
<td>0.142</td>
<td>0.261</td>
</tr>
<tr>
<td>Corrected QT (msc)</td>
<td>0.123</td>
<td>0.121</td>
<td>0.245</td>
<td>0.049</td>
</tr>
<tr>
<td>QT dispersion (msc)</td>
<td>0.070</td>
<td>0.380</td>
<td>0.138</td>
<td>0.276</td>
</tr>
<tr>
<td>P-wave dispersion (msc)</td>
<td>0.284</td>
<td>&lt; 0.0001</td>
<td>0.275</td>
<td>0.031</td>
</tr>
<tr>
<td>Ejection fraction (%)</td>
<td>- 0.182</td>
<td>&lt; 0.05</td>
<td>- 0.309</td>
<td>0.013</td>
</tr>
</tbody>
</table>

A comparison between the electrocardiographic parameters and ejection fraction in both genders revealed that PWD was higher and the ejection fraction was lower in the male group (Table 2).

Table 2. Comparison of electrocardiographic parameters and ejection fraction between female and male patients.

<table>
<thead>
<tr>
<th></th>
<th>Female (n = 80)</th>
<th>Male (n = 174)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>64.6 ± 8.3</td>
<td>58.5 ± 10.5</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>GGT activity (u/l)</td>
<td>30.1 ± 21.3</td>
<td>41 ± 33.4</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Sokolow-Lyon voltage (mm)</td>
<td>18.7 ± 8.9</td>
<td>20.1 ± 9.1</td>
<td>0.283</td>
</tr>
<tr>
<td>Cornell voltage (mm)</td>
<td>13.9 ± 6.2</td>
<td>15.2 ± 6.9</td>
<td>0.191</td>
</tr>
<tr>
<td>Cornell product (mm.sc)</td>
<td>1263.0 ± 767.8</td>
<td>1378.9 ± 818.1</td>
<td>0.323</td>
</tr>
<tr>
<td>Corrected QT (msc)</td>
<td>421.7 ± 54.6</td>
<td>407.2 ± 67.7</td>
<td>0.123</td>
</tr>
<tr>
<td>QT dispersion (msc)</td>
<td>39.3 ± 19.4</td>
<td>44.6 ± 31.8</td>
<td>0.215</td>
</tr>
<tr>
<td>P-wave dispersion (msc)</td>
<td>30.1 ± 14.7</td>
<td>39.9 ± 39.4</td>
<td>0.045</td>
</tr>
<tr>
<td>Ejection fraction (%)</td>
<td>56.0 ± 10.8</td>
<td>53.0 ± 12.2</td>
<td>0.088</td>
</tr>
</tbody>
</table>

Similarly, it was found that there was a positive correlation of GGT activity with PWD in the nonsmoker group (r = 0.360, p < 0.0001), but it correlated negatively with the EF in the same group (r = -0.211, p = 0.028). On the other hand, GGT activity only correlated with PWD in the smoker subgroup (r = 0.194, p = 0.045).

Reproducibility analysis results were as follows: Intra-observer variability was 2.4% for Sokolow-Lyon voltage criteria, 3.1% for Cornell voltage criteria, 4.9% for Cornell product, 5.0% for QT dispersion, 5.7% for P-wave dispersion, 4.6% for Ejection fraction. Inter-observer variability was 3.5% for Sokolow-Lyon voltage criteria, 3.8% for Cornell voltage criteria, 6.2% for Cornell product, 6.5% for QT dispersion, 6.4% for P-wave dispersion, 7.3% for Ejection fraction.

4. Discussion
A variety of research studies have determined raised GGT activity in the progression of atherosclerosis, which is associated with oxidative stress (Paolicchi et al., 2004; Emmin et al., 2005; Ulus et al., 2007; Bradley et al., 2014). GGT appears to be a strong predictor of acute coronary events besides cardiovascular risk factors. Epidemiological evidence from recent studies demonstrates that GGT, which is generally used in hepatobiliary disease and the use of alcohol, can be used as a prognostic marker for mortality and morbidity from cardiovascular disease (Karlson et al., 2000, Emdin et al., 2001; Ruttmann et al., 2005; Wannamethee et al., 2008).

There are studies suggesting that GGT is a predictor of cardiac mortality or non-fatal myocardial infarction, especially in patients who had ischemia which was identified as coronary atherosclerosis, and a history of myocardial infarction (Paolicchi et al., 2004; Ruttmann et al., 2005; Lee et al., 2007; Lee et al., 2009, Patterson et al., 2015).

The studies, which were carried out on an apparently healthy general population, demonstrate that GGT is a strong predictor of acute coronary events,
independently of other cardiovascular risk factors (Lee et al., 2006; Meisinger et al., 2006; Kunutsor et al., 2015).

Our results demonstrate that GGT activity only relates to one of the non-invasive arrhythmia indicators, PWD. In our study, higher PWD but lower EF was found in male compared to female patients. Assessment of smoking and nonsmoking patients based on the GGT activity showed that GGT activity was associated with PWD in both of the groups.

Prolongation of interatrial and intraatrial conduction, along with nonhomogeneous conduction of sinus stimulus, is considered an indicator of atrial fibrillation risk (Dilaveris et al., 2000; Tukek et al., 2001; Perzanowski et al., 2005). It is known that increased PWD and prolongation of maximum P-wave duration are non-invasive signs of heterogeneous and unstable electric activity, and this can trigger atrial reentry. Prolongation of the P-wave duration reflects the changes to the atrial substrate. Even though there is a higher prevalence of coronary artery disease in patients with atrial fibrillation (Kannel et al., 1982; Krahn et al., 1995; Lip and Beever, 1995), atrial fibrillation is less prevalent in patients with CAD (Haddad et al., 1978; Cameron et al., 1988). Numerous studies note the role of inflammation (Aviles et al., 2003; Van Wagoner, 2008; Ozaydin, 2010) and the rise in C-reactive protein levels in atrial fibrillation patients (Chung et al., 2001; Watanabe et al., 2005). Similarly, it is reported that systolic dysfunction rather than ischemia may lead to atrial fibrillation in coronary artery disease patients (Lokshyn et al., 2000). Left ventricle dysfunction can lead to the development of atrial fibrillation due to electro-mechanic feedback and neurohormonal activation (Van den Berg et al., 1997). When increased oxidative stress in atrial fibrillation is considered (Neuman et al., 2007), the association between PWD and GGT activity suggests that the oxidative process is effective in the development of atrial fibrillation. The positive correlation between GGT and PWD and the negative correlation between GGT and EF are parallel findings in our study. These findings can be explained by the frequent concomitance of decreased left ventricle function and atrial arrhythmias. There are studies showed that association of GGT activity and atrial fibrillation. (Tekin et al., 2013; Alonso et al., 2014)

In this study, we found that increased GGT activity was correlated with P-wave dispersion. These results indicate that there might be an increased risk of arrhythmias especially the atrial fibrillation in this patient population. However, prospective, larger and long-term studies are necessary to obtain more accurate conclusions.

REFERENCES


